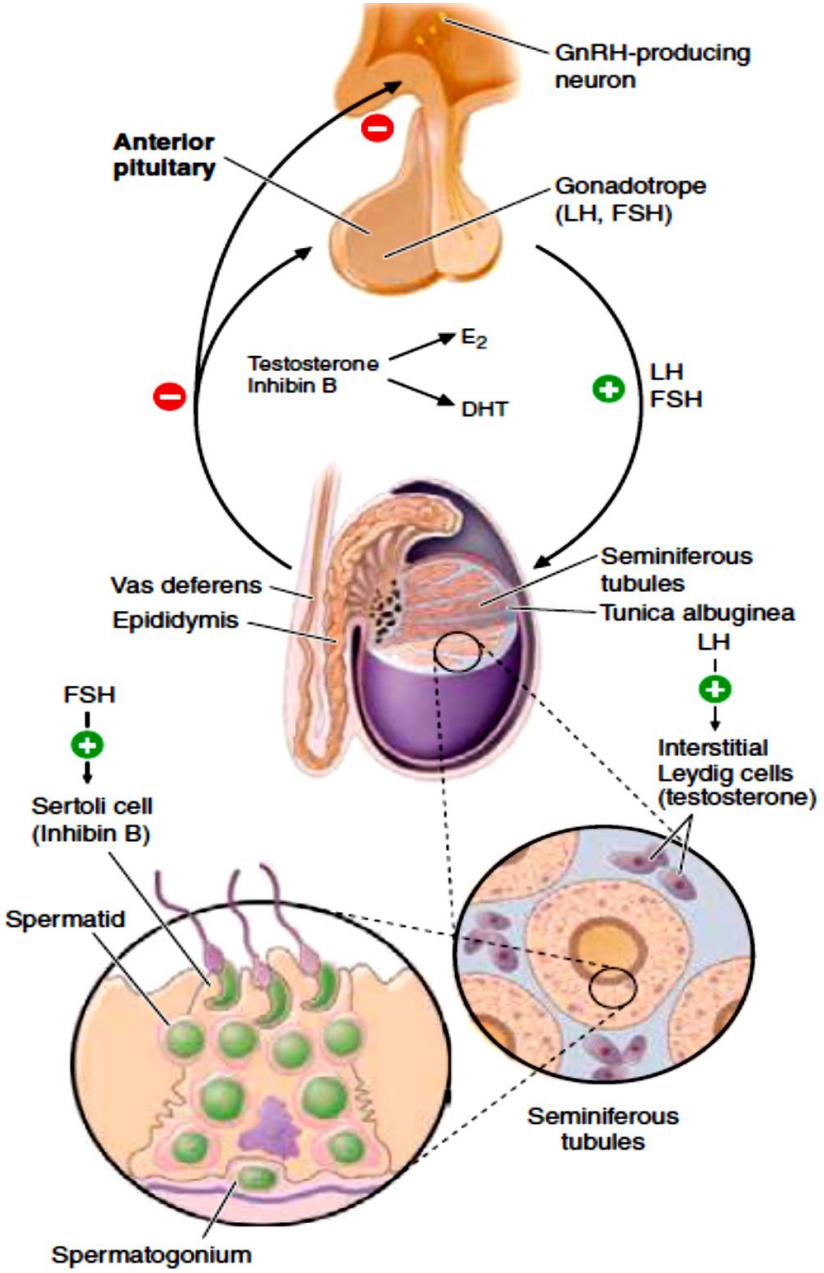
Male Reproductive Endocrinology

M.A. Keshavarz M.D.
Assistant of Professor of Endocrinology
Qazvin University of Medical Sciences

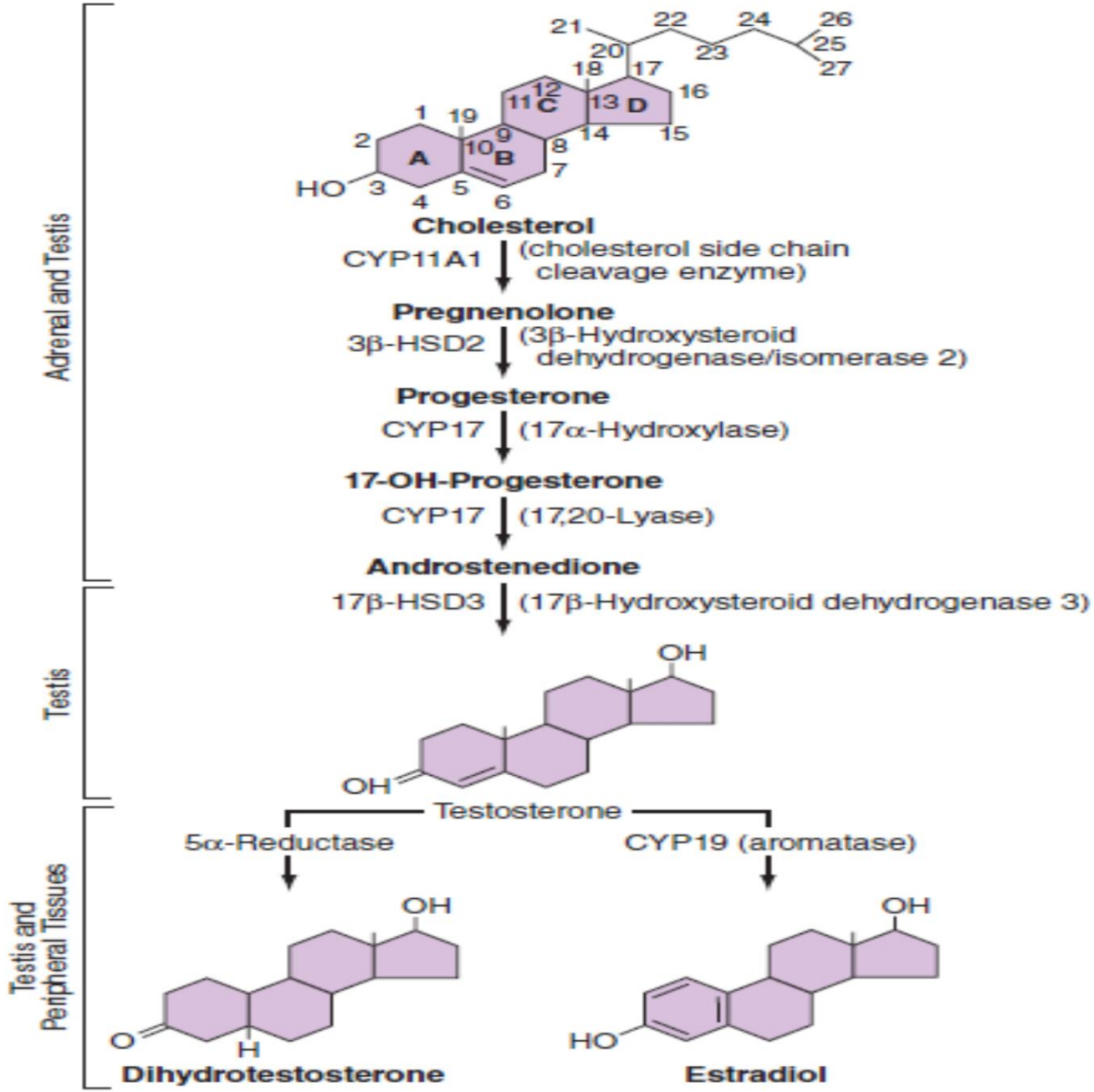
- The fetal testis develops from the undifferentiated gonad after expression of a genetic cascade that is initiated by the SRY (sex-related gene on the Y chromosome)

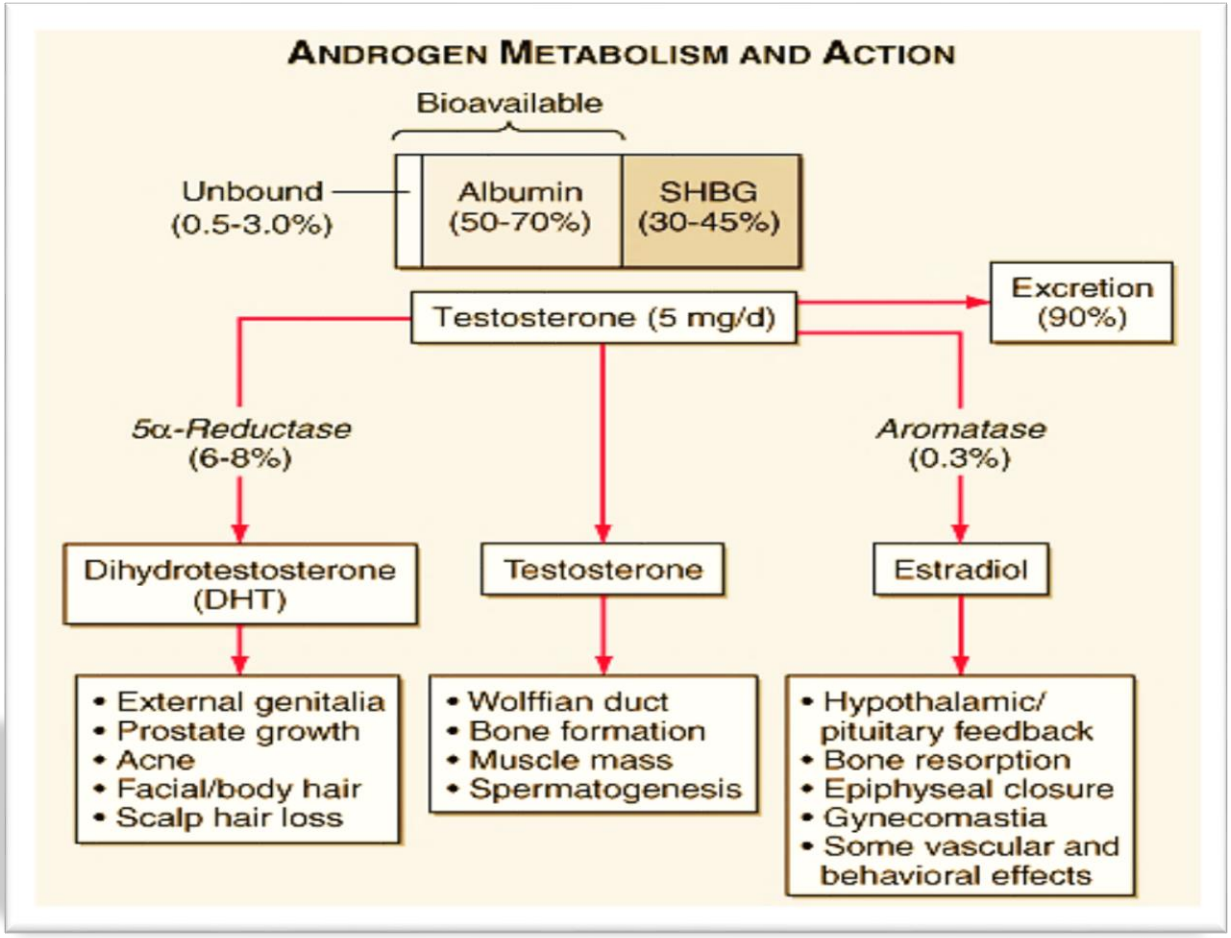
- The testes are composed of Leydig (interstitial) cells, which secrete testosterone and estradiol, and the seminiferous tubules, which produce sperm…

- They are regulated by the luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are secreted by the anterior pituitary under the influence of the hypothalamic deca-peptide GnRH…



- Leydig cells produce testosterone, which supports the growth and differentiation of wolffian duct structures that develop into the epididymis, vas deferens, and seminal vesicles…
- Testosterone is also converted to DHT, which induces formation of the prostate and the external male genitalia, including the penis, urethra, and scrotum …
- Testicular descent through the inguinal canal is controlled in part by Leydig cell production of insulin-like factor 3 (INSL3), …
- Sertoli cells produce müllerian inhibiting substance (MIS), which causes regression of the müllerian structures, including the fallopian tube, uterus, and upper segment of the vagina…


Adrenal and Testis
Testis
Testis and Peripheral Tissues
Cholesterol
CYP11A1
(cholesterol side chain cleavage enzyme)
Pregnenolone
3β-HSD2
(3β-Hydroxysteroid dehydrogenase/isomerase 2)
Progesterone
CYP17
(17α-Hydroxylase)
17-OH-Progesterone
CYP17
(17,20-Lyase)
Androstenedione
17β-HSD3
(17β-Hydroxysteroid dehydrogenase 3)
Testosterone
5α-Reductase
CYP19 (aromatase)
Dihydrotestosterone
Estradiol



- Estrogen, hyperthyroidism, many chronic inflammatory illnesses, and aging are associated with high SHBG concentrations …

- SHBG concentrations are decreased by androgens, obesity, insulin, and nephrotic syndrome…

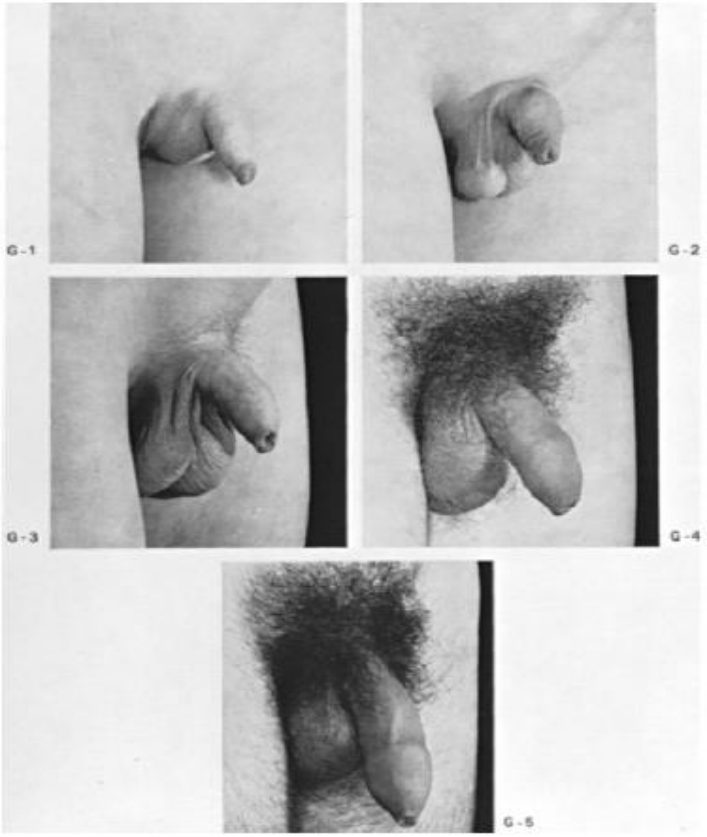
- The development of secondary sex characteristics is initiated by adrenarche, which usually occurs between 6 and 8 years of age when the adrenal gland begins to produce greater amounts of androgens from the zona reticularis, the principal site of DHEA production…

- The GnRH pulse generator in the hypothalamus is active during fetal life and early infancy but is quiescent until the early stages of puberty, when the sensitivity to steroid inhibition is gradually lost, causing reactivation of GnRH secretion…

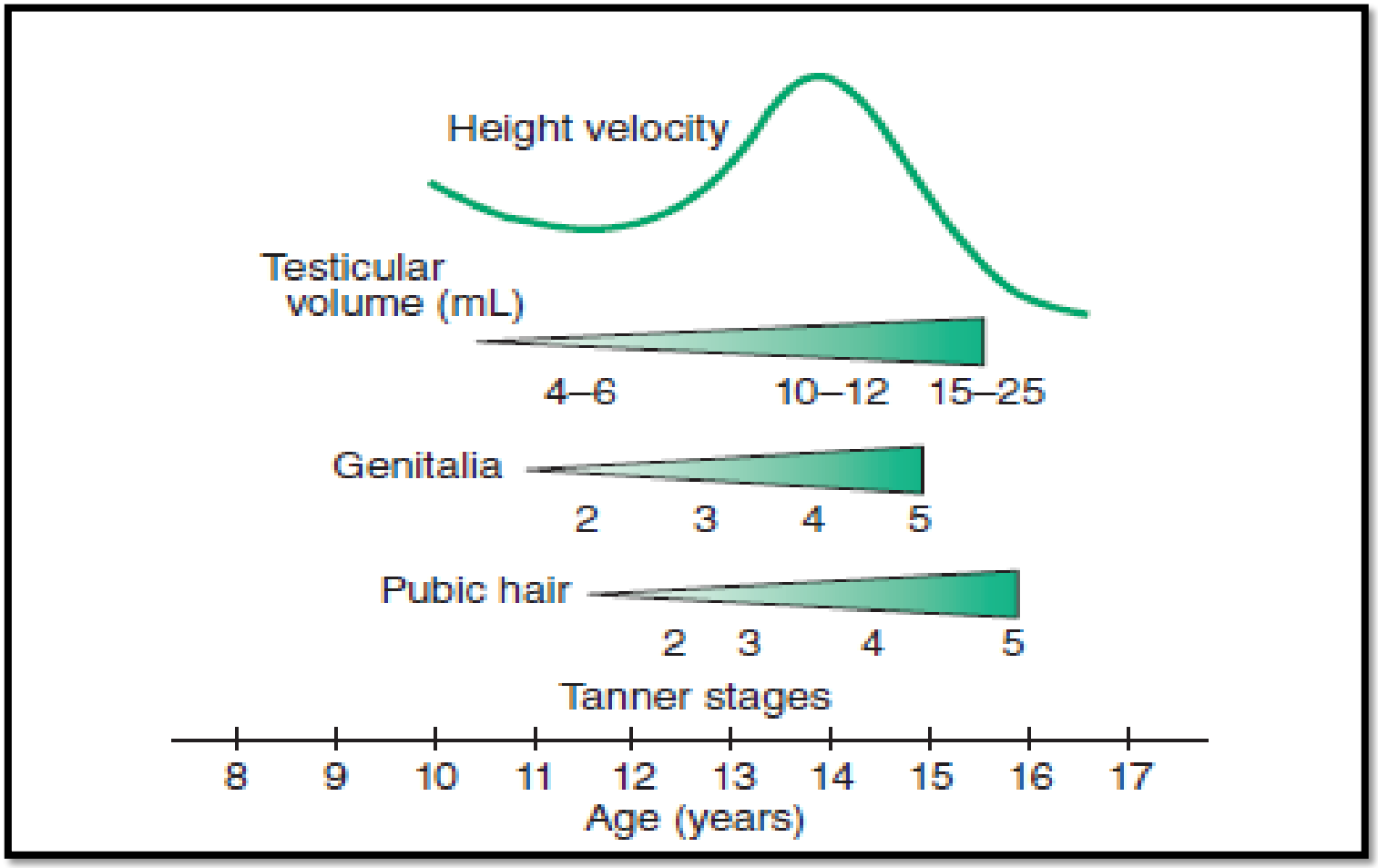
- The early stages of puberty are characterized by nocturnal surges of LH and FSH…

Stages of male genital development according to Marshall and Tanner

- Stage 1: preadolescent; Testes, scrotum, and penis are about the same size and proportion as in early childhood.
- Stage 2: the scrotum and testes have enlarged; the scrotal skin shows a change in texture and some reddening.
- Stage 3: growth of the penis has occurred; at first mainly in length but with some increase in breadth; there is further growth of the testes and scrotum.
- Stage 4: the penis is further enlarged in length and breadth, along with development of the glans. The testes and scrotum are further enlarged. The scrotal skin has further darkened.
- Stage 5: genitalia are adult in size and shape. No further enlargement takes place after stage 5 is reached…



Normal pubertal development



Delayed Puberty

- Puberty is delayed in boys if it has not ensued by age 14, an age that is 2–2.5 standard deviations above the mean for healthy children…

- There are four main categories of delayed puberty:

  1) Constitutional delay of growth and puberty (~60% of cases);

  2) Functional hypogonadotropic hypogonadism caused by systemic illness or malnutrition (~20% of cases);

  3) Hypogonadotropic hypogonadism caused by genetic or acquired defects in the hypothalamic-pituitary region (~10% of cases);

  4) Hyper-gonadotropic hypogonadism secondary to primary gonadal failure (~15% of cases)

Approach to the Patient with Delayed Puberty

- Any history of systemic illness, eating disorders, excessive exercise, social and psychological problems, and abnormal patterns of linear growth during childhood should be verified…
- Physical examination should focus on height; arm span; weight; visual fields; and secondary sex characteristics, including hair growth, testicular volume, phallic size, and scrotal reddening and thinning…
- Testicular size >2.5 cm generally indicates that the child has entered puberty…

- The main diagnostic challenge is to distinguish those with constitutional delay, who will progress through puberty at a later age, from those with an underlying pathologic process…
- Constitutional delay has suspected when there is a *family history* and when there are *delayed bone age and short stature*…
- Blunted responses to exogenous GnRH can be seen in patients with constitutional delay, GnRH deficiency, or pituitary disorders…
- Thus, constitutional delay is a diagnosis of exclusion that requires ongoing evaluation until the onset of puberty and the growth spurt…

- The clinical manifestations of androgen deficiency depend on the time of onset and the degree of deficiency…
- Early pre-natal androgen deficiency leads to the formation of ambiguous genitalia and to male pseudo-hermaphroditism…
- Androgen deficiency occurring later during gestation may result in micropenis or cryptorchidism…
- Prepubertal androgen deficiency leads to poor muscle development, decreased strength and endurance, a high-pitched voice, sparse axillary and pubic hair, and the absence of facial and body hair.
- Post pubertal androgen deficiency may result in a decrease in libido, impotence, low energy, fine wrinkling around….

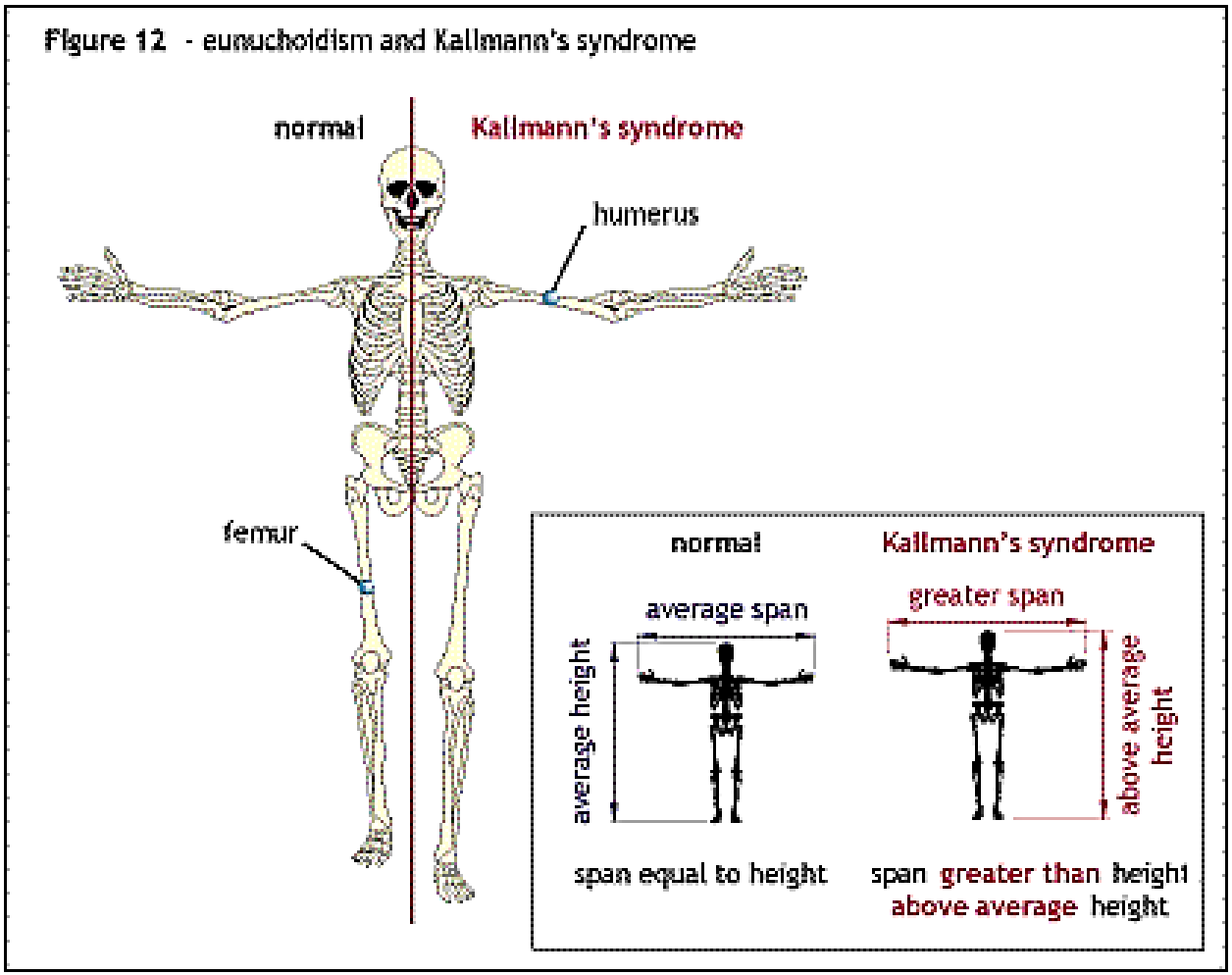
Biochemical evaluation

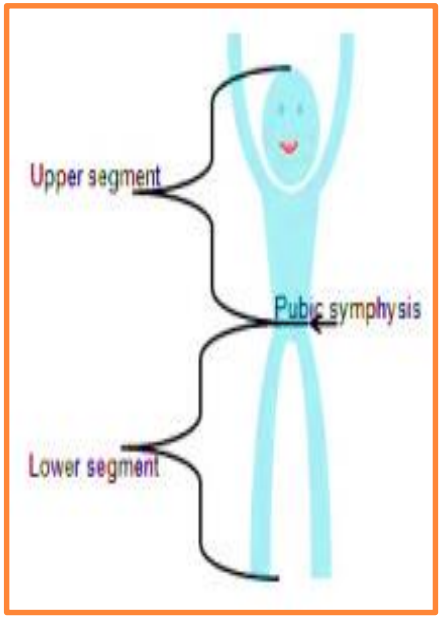
- In men with a low testosterone & LH level can distinguish primary (high LH) versus secondary (low or inappropriately normal LH) hypogonadism…
- Increased FSH suggests damage to the seminiferous tubules…
- Inhibin B a Sertoli cell product that suppresses FSH, is reduced with seminiferous tubule damage…
- GnRH stimulation testing is used rarely except to evaluate gonadotrope function in patients who have undergone pituitary surgery or have a space occupying lesion in the hypothalamic-pituitary region…
- A minimally acceptable response is a two-fold LH increase and a 50% FSH increase…

HCG Stimulation Test

- The hCG stimulation test is performed by administering a single injection of 1500–4000 IU of hCG intramuscularly and measuring testosterone levels at baseline and 24, 48, 72, and 120 h after hCG injection…
- An acceptable response to hCG is a doubling of the testosterone concentration in adult men.
- In prepubertal boys, an increase in testosterone to >150 ng/dL indicates the presence of testicular tissue.
- No response may indicate an absence of testicular tissue or marked impairment of Leydig cell function.

- The long bones of the lower extremities and arms may continue to grow under the influence of growth hormone; this condition leads to eunuchoid proportions (arm span exceeding total height by ≥5 cm) and greater growth of the lower extremities relative to total height….





Bone age

2 yrs 6 m.

10 yrs

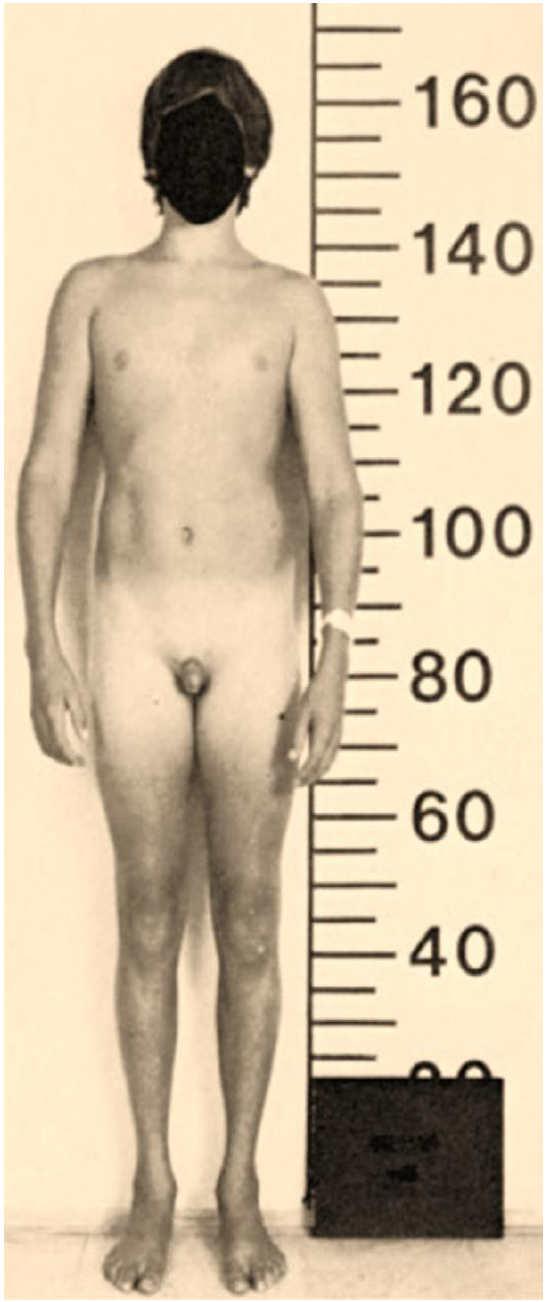
12 yrs

TABLE 65-1 CLASSIFICATION OF MALE HYPOGONADISM

HYPOTHALAMIC-PITUITARY DISORDERS (SECONDARY HYPOGONADISM)
Panhypopituitarism
Isolated gonadotropin deficiency
Complex congenital syndromes
Hyperprolactinemia
Hypothalamic dysfunction
GONADAL DISORDERS (PRIMARY HYPOGONADISM)
Klinefelter's syndrome and associated chromosomal defects
Myotonic dystrophy
Cryptorchidism
Bilateral anorchia
Seminiferous tubular failure
Adult Leydig cell failure
Androgen biosynthesis enzyme deficiency
DEFECTS IN ANDROGEN ACTION
Testicular feminization (complete androgen insensitivity)
Incomplete androgen insensitivity
5α-Reductase deficiency

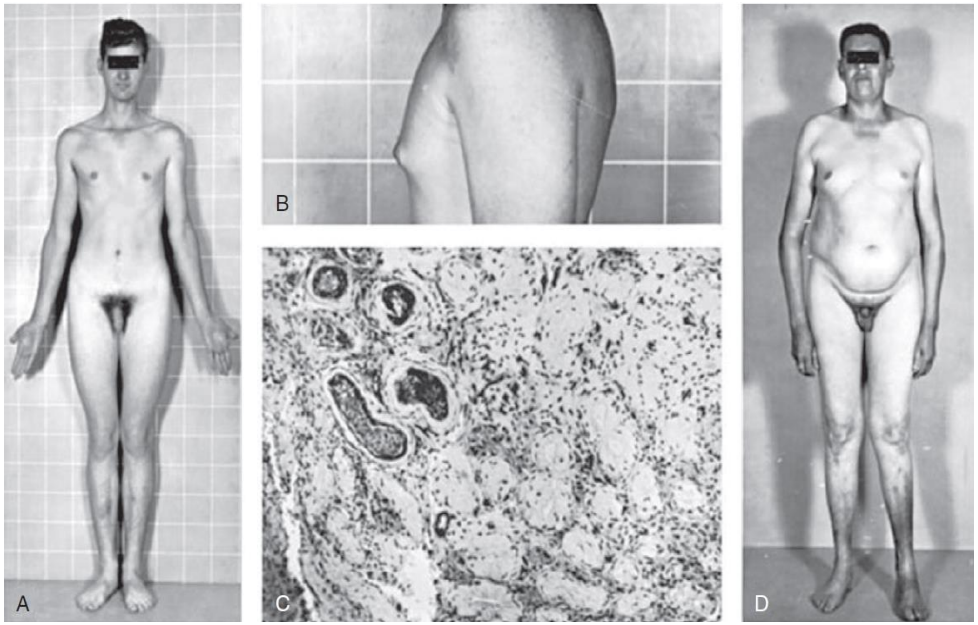
- **Kallmann syndrome** is a form of hypogonadotropic hypogonadism that results from a **defect in the migration of the GnRH neurons** from the olfactory placode into the hypothalamus and is associated with problems in the ability to discriminate odors, either incompletely (hyposmia) or completely (anosmia)…

- The upper-to-lower body ratio was 0.86… which is eunuchoid…



- **Klinefelter's syndrome** *is* the most common congenital cause of primary testicular failure *which occurs in about 1 of every 600 live* male births and is usually caused by a maternal meiotic chromosomal nondisjunction that results in an XXY genotype…

- At puberty, clinical findings include the following: a variable degree of hyper-gonadotropic hypogonadism; gynecomastia; small, firm testes measuring less than 2 cm in the longest axis; azoospermia; and eunuchoid skeletal proportions…



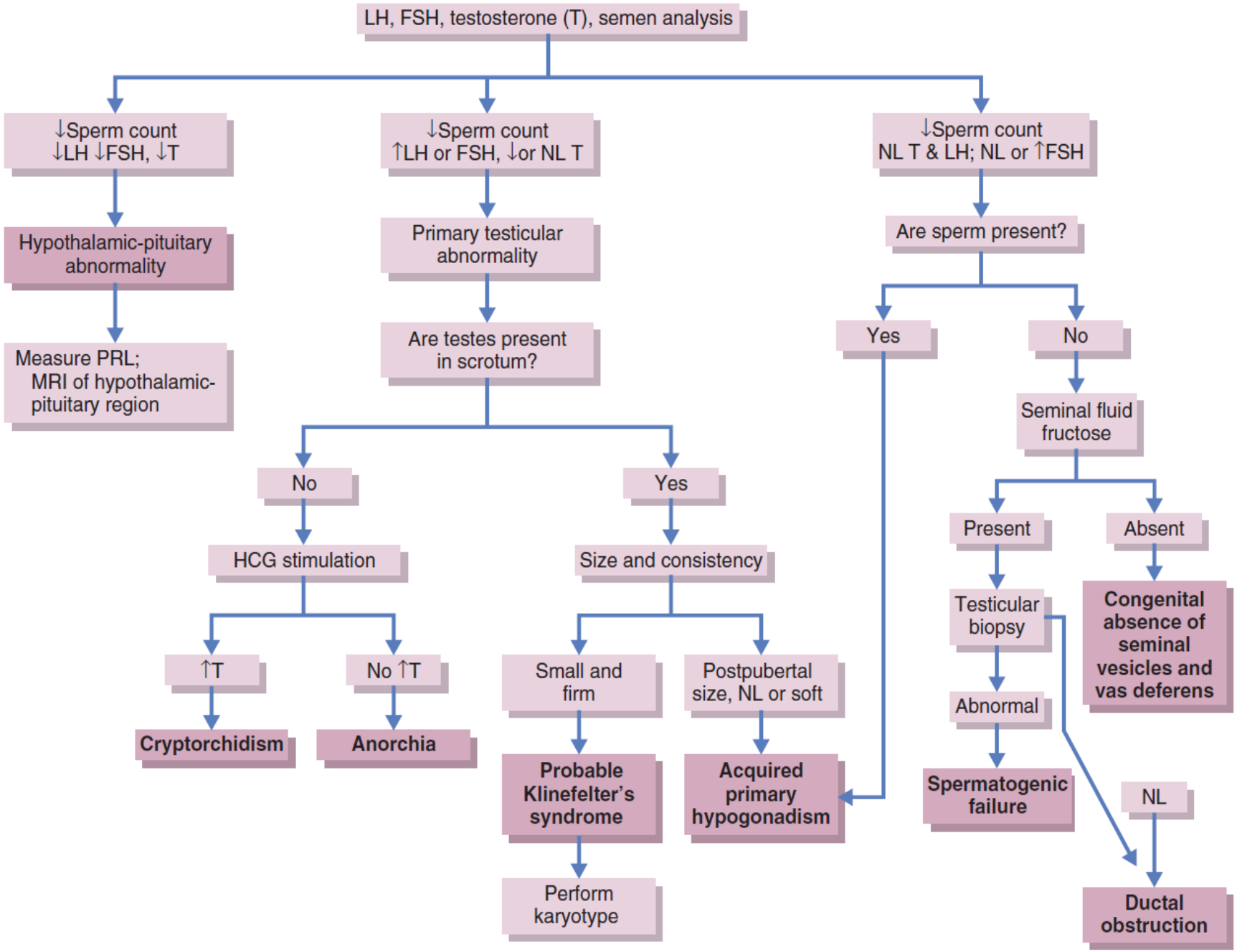
- About 3% of full-term male infants have *cryptorchidism*, *which* spontaneously corrects during the first year of life in most cases…

- Bilateral anorchia, also known as the vanishing testicle syndrome, is a rare condition in which the external genitalia are fully formed, however, the testicular tissue disappears before or shortly after birth, and the result is an empty scrotum…

- This condition is differentiated from cryptorchidism by an HCG stimulation test…

- The adult seminiferous tubules and leydig cell compartment are susceptible to a variety of injuries:
  - infections (mumps, gonococcal or lepromatous orchitis)
  - irradiation,
  - vascular injury,
  - trauma,
  - alcohol ingestion,
  - chemotherapeutic drugs (especially alkylating agents)
- Some men experience a gradual decline in testicular function as they age, possibly because of microvascular insufficiency…

- An absence of androgen receptors causes the syndrome of testicular feminization, a form of male pseudo-hermaphroditism…
- The serum testosterone concentrations are elevated as a result of continuous stimulation by elevated concentrations of LH…
- Because androgens are inactive during embryogenesis, the labial-scrotal folds fail to fuse, and a short vagina results.
- These genetic males have cryptorchid testes but appear to be phenotypic females and the fallopian tubes, uterus, and upper portion of the vagina are absent because the testes secrete müllerian duct inhibitory factor during early fetal development…
- At puberty, these patients have breast enlargement and axillary and pubic hair does not grow…


LH, FSH, testosterone (T), semen analysis
↓Sperm count
↓LH ↓FSH, ↓T
Hypothalamic-pituitary abnormality
Measure PRL; MRI of hypothalamic-pituitary region
↓Sperm count
↑LH or FSH, ↓or NL T
Primary testicular abnormality
Are testes present in scrotum?
No
HCG stimulation
↑T
No ↑T
Cryptorchidism
Anorchia
Yes
Size and consistency
Small and firm
Postpubertal size, NL or soft
Probable Klinefelter's syndrome
Perform karyotype
Acquired primary hypogonadism
↓Sperm count
NL T & LH; NL or ↑FSH
Are sperm present?
Yes
No
Seminal fluid fructose
Present
Absent
Congenital absence of seminal vesicles and vas deferens
Testicular biopsy
Abnormal
Spermatogenic failure
NL
Ductal obstruction

Treatment

- If therapy is considered appropriate, it can begin with 25–50 mg testosterone enanthate or testosterone cypionate every 2 weeks, or by using a 2.5-mg testosterone patch or 25-mg testosterone gel.
- Because aromatization of testosterone to estrogen is obligatory for mediating androgen effects on epiphyseal fusion, concomitant treatment with aromatase inhibitors may allow attainment of greater final adult height….
- Testosterone treatment should be interrupted after 6 months to determine if endogenous LH and FSH secretion have ensued…

PRECOCIOUS PUBERTY

- Puberty in boys before age 9 is considered precocious…

Gonadotropin-dependent Precocious Puberty

- Central precocious puberty (CPP), is less common in boys than in girls…
- It is caused by premature activation of the GnRH pulse generator, sometimes because of central nervous system (CNS) lesions such as hypothalamic hamartomas, but it is often idiopathic…
- MRI should be performed to exclude a mass, structural defect, infection, or inflammatory process.

  - ✓ Always isosexual…!
  - ✓ Bone age is accelerated…
  - ✓ FSH and LH elevation after LH-RH is diagnostic test (LH/FSH > 2)
  - ✓ MRI of CNS is necessary to exclude the neoplasia

GONADOTROPIN-INDEPENDENT PRECOCIOUS PUBERTY

- Androgens from the testis or the adrenal are increased but, gonadotropins are low…

- **This group of disorders includes:**
  - hCG -secreting tumors
  - congenital adrenal hyperplasia (CAH)
  - sex steroid–producing tumors of the testis and adrenal
  - accidental or deliberate exogenous sex steroid administration
  - activating mutations of the LH receptor or Gs-α subunit …

Familial Male-Limited Precocious Puberty

- Also called testotoxicosis, familial male-limited precocious puberty is an autosomal dominant (AD) disorder caused by activating mutations in the LH receptor, leading to constitutive stimulation of the c-AMP pathway and testosterone production
- Clinical features include premature androgenization in boys, growth acceleration in early childhood, and advanced bone age followed by premature epiphyseal fusion…
- Testosterone is elevated, and LH is suppressed…
- Treatment : inhibitors of testosterone synthesis (e.g., ketoconazole), androgen receptor antagonists (e.g., flutamide), and aromatase inhibitors (e.g., anastrazole)

Approach to the Patient with Precocious Puberty

- After verification of precocious development, serum LH and FSH levels should be measured to determine the gonadotropin-dependent or gonadotropin-independent precocious puberty …

- In children with gonadotropin-dependent precocious puberty, CNS lesions should be excluded by history, neurologic examination, and MRI scan of the head.

- If organic causes are not found, one is left with the diagnosis of idiopathic central precocity…

- Patients with high testosterone but suppressed LH concentrations have gonadotropin-independent sexual precocity…

- In these patients, DHEAS and 17 –hydroxyl-progesterone should be measured…

  - High levels of testosterone and 17 -hydroxyprogesterone suggest the possibility of CAH due to 21- or 11-hydroxylase deficiency…

  - If testosterone and DHEAS are elevated, adrenal tumors should be excluded by obtaining a CT scan of the adrenal glands…

- Patients with elevated testosterone but without increased 17 –(OH)P or DHEAS should undergo careful evaluation of the testis by palpation and ultrasound to exclude a Leydig cell neoplasm…

Gynecomastia

- Gynecomastia refers to a benign enlargement of the male breast that results from proliferation of the glandular component.
- This common condition is found in as many as 70% of pubertal boys and in about one third of adults 50 to 80 years old.
- Painful and tender gynecomastia in a pubertal adolescent should be monitored with periodic examinations because, in most patients, pubertal gynecomastia disappears within 1 year…
- Incidentally discovered, asymptomatic gynecomastia in an adult requires a careful assessment for alcohol, drug, or medicationuse, liver, lung, or kidney dysfunction and signs and symptoms of hypogonadism or hyperthyroidism…

- Removal of the offending drug or correction of the underlying condition causing the gynecomastia may result in regression of the breast glandular tissue…
- If the gynecomastia persists, a trial of antiestrogens (e.g., tamoxifen) may be given for 3 months to see whether regression occurs…
- Gynecomastia that has been present for longer than 1 year usually contains a fibrotic component that does not respond to medications…
- In these cases, correction usually requires surgical removal of the tissue…

TABLE 65-2 CONDITIONS ASSOCIATED WITH GYNECOMASTIA

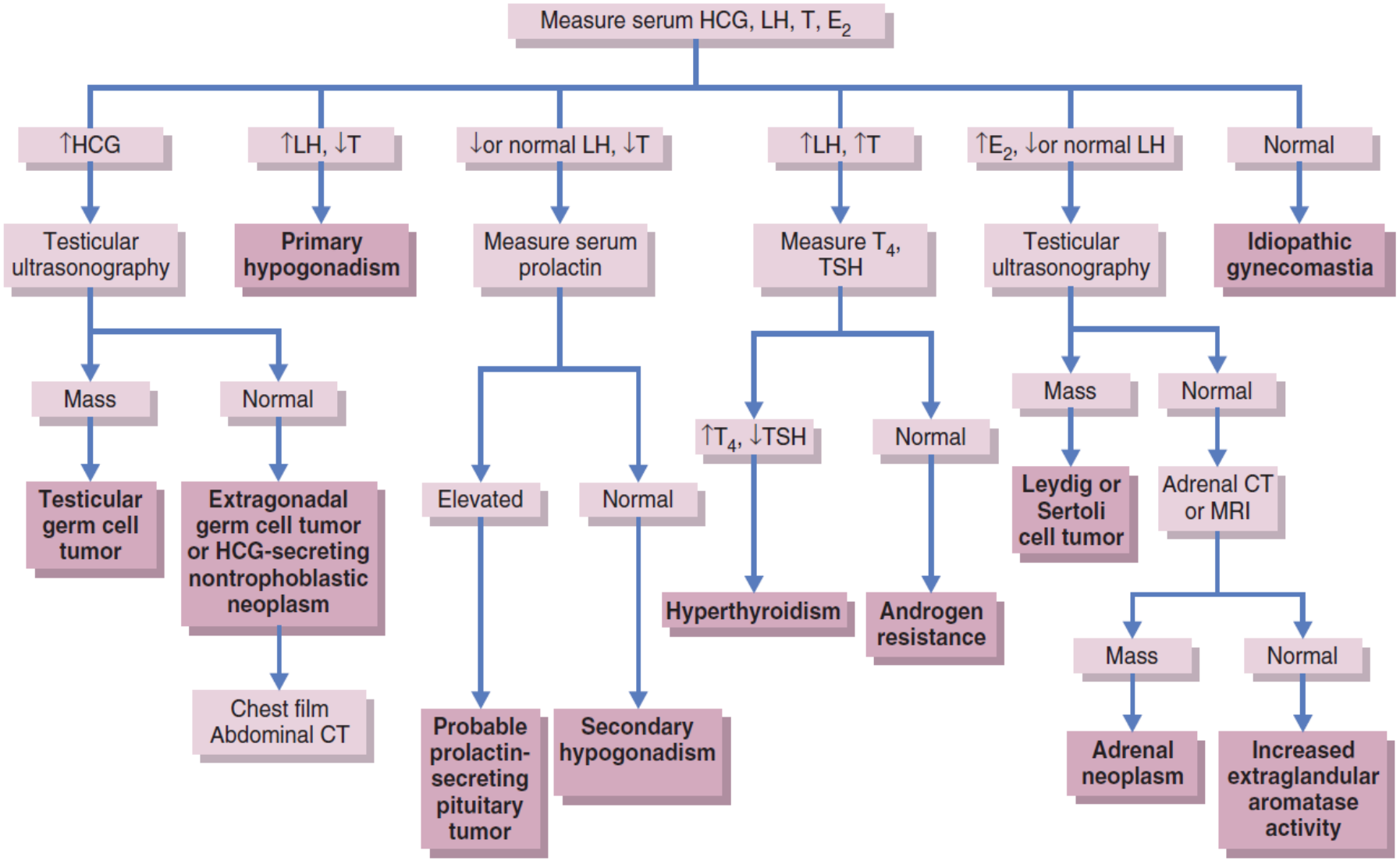
PHYSIOLOGIC CONDITIONS

- Neonatal
- Pubertal
- Involutional

PATHOLOGIC CONDITIONS

- Neoplasms
  - Testicular
  - Adrenal
  - Ectopic production of human chorionic gonadotropin
- Primary gonadal failure
- Secondary hypogonadism
- Enzyme defects in testosterone production
- Androgen insensitivity syndromes
- Liver disease
- Malnutrition with refeeding
- Dialysis
- Hyperthyroidism
- Excessive extraglandular aromatase activity
- Drugs
  - Estrogens and estrogen agonists
  - Gonadotropins
  - Antiandrogens or inhibitors of androgen synthesis
  - Cytotoxic agents
  - Efavirenz
- Alcohol
- Human immunodeficiency virus infection
- Idiopathic

- Male breast Cancer usually manifests as a unilateral, eccentric, hard or firm mass that is fixed to the underlying tissues...
- Although physical examination is usually sufficient to differentiate gynecomastia from breast carcinoma, mammography may be required….



Diagnostic evaluation for causes of gynecomastia based on measurements of serum HCG, LH, testosterone, and estradiol, T4 and TSH…